FACTORS INFLUENCING DEVELOPMENT OF SCROTUM

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ONE PLATE (FIVE FIGURES)

It is generally known that the scrotum plays an important physiological role inasmuch as it helps to regulate testis temperature which in turn influences spermatogenesis. Yet much less attention has been given to the hormonal regulation of the scrotum than to that of the other accessory sex organs. It has been established that in the immature rodent (Steinach and Kun, '40; Hamilton, '36) or monkey (Hamilton, '38) as well as in cryptorchid human beings (McCullagh and McGurl, '39; Kearns, '39) treatment with testosterone and other testoid compounds causes a descent of the testis into the scrotum with a corresponding increase in the size of the latter. However, these observations cannot answer the question whether the testoids act on the scrotum directly, or through the intermediary of the testis which distends the scrotum by its mere descent. The studies of Phillips ('38), Phillips and Andrews ('36), Andrews ('40) and Tyrrell, Andrews and Zelle ('42) led them to conclude that the mere mechanical presence of the testis plays no part in maintaining the scrotum in a physiologically normal condition and that the internal secretion of the gonad is the sole regulator of scrotal activity. They arrived at this conclusion by physiological experiments indicating that after castration the contractility of the tunica dartos muscles is severely damaged and cannot be maintained by substituting steel balls for the gonads.

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Although these experiments convincingly show that the mere presence of a heavy foreign body does not suffice to cause normal scrotal development, they do not prove that mechanical factors are not involved in the development of this organ. From numerous observations made in this laboratory on castrate rats treated with large doses of various testoid compounds the impression was gained that even if the treatment caused the seminal vesicles and prostates to undergo enormous development it never resulted in the formation of a normal scrotum. In the writer's opinion the experiments described in this communication show that both hormonal and mechanical factors play a role in scrotal development.

EXPERIMENTAL

In the first experiment twenty immature albino rats weighing 26–40 gm. (average 33 gm.) were castrated through a suprapubic incision after placing a single ligature around the blood vessels and vasa deferentia of both testes. The epididymis was removed with the gonad. These technical details are emphasized because if a castration is performed in this manner scar tissue develops, forming a bridge between the two spermatic cords, which actually pulls on the gubernaculum testis and hence counteracts any possible pressure that the intra-abdominal organs may exert on the inguinal canal and the region from which the scrotum will subsequently be formed. It should also be pointed out that at the time of castration the testes of these animals had not descended and hence a scrotum was not developed as yet. Immediately after castration the animals were divided into two groups of ten. The first group remained untreated while the second group received bidaily subcutaneous injections of 500 γ of testosterone in 0.1 cc. of peanut oil. One month after initiation of the treatment all animals were killed. It was found that at this time neither the castrate controls nor the testosterone treated castrates showed any sign of scrotum development, although the seminal vesicles of the treated animals averaged 500 mg. (range 412–552 mg.) and the prostates 296 mg. (range

244–406 mg.) as compared with an average weight of 13 mg. (range 11–16 mg.) for the seminal vesicles and 19 mg. (range 13–29 mg.) for the prostates of the untreated controls. It may be said that the seminal vesicles and prostates of the treated castrates were actually larger than those of intact males of the same age, yet their scrotum remained undeveloped, while that of normal males of the same age and weight is invariably fully formed (fig. 1).

Thus it appears that in the absence of testicular tissue a disproportion exists between the ability of testosterone to stimulate the seminal vesicles and prostates and its inability to cause scrotal development. It was hence decided to investigate whether the hormone could prevent the scrotal atrophy which normally occurs after castration in post-pubertal rats. Twenty albino rats weighing 115–140 gm. (average 127 gm.) were castrated using the same technic as in the previous experiment.

Immediately after castration the animals were subdivided into two groups of ten. The first group remained untreated while the second group received bidaily subcutaneous injections of 2.5 mg. of testosterone propionate in 0.1 cc. of peanut oil. In this series the more active propionate was used and given in a considerably higher dose than was employed in the first experiment because the animals were correspondingly larger. Treatment was continued for 75 days. At the end of this period the scrotum of both groups was significantly smaller than that of intact normal males of the same age in our colony. However, the involution of the scrotum was less pronounced in the treated than in the untreated castrates. The seminal vesicles of the treated animals averaged 1387 mg. (range 1116–1746 mg.) and the prostates 906 mg. (range 665–1143 mg.) as compared with an average weight of 39 mg. (range 20–61 mg.) for the seminal vesicles and 31 mg. (range 26–36 mg.) for the prostates of the untreated controls. The seminal vesicles and prostates of our treated castrates were considerably larger than those of intact males of the same age. Yet some involution of the scrotum undoubtedly oc-

curred as a result of castration. Hence it appears that even excessive doses of testoid compounds cannot completely prevent scrotal involution following gonadectomy (fig. 2).

A third experiment was then conducted on thirty very young albino males weighing 21–28 gm. (average 25 gm.). Ten of these animals were castrated after placing a separate ligature around the pedicle of each testis so as to prevent any traction on the gubernaculum. In these the epididymis was removed together with the testis. A second group of ten animals was gonadectomized by severing the communication between testis and epididymis leaving the latter intact. The remaining ten animals were similarly castrated but an "artificial testis" was substituted for the gonad. Such artificial testes were made from glass tubing which had a diameter of 7 mm. and was cut into pieces of 1.7 cm. in length. The sharp edges of the tubing were rounded off in the flame of a Bunsen burner and a silk thread was led through the lumen. With aid of this thread the beads were sewn on to the head of the epididymis on one side and to the tail of the organ on the other side. In this manner they occupied the natural position of the testis which of course at this time was still above the inguinal canal. Immediately after these various operations all thirty animals were treated with bidaily subcutaneous injections of 500 γ of testosterone propionate in 0.1 cc. of peanut oil for 1 month. At the end of this period scrotum development was very slight in the animals of the first group (testis and epididymis removed) but practically normal in those of the second (only testis removed) and third (testis substituted by glass bead) groups. It is believed that the moderate degree of scrotal development which occurred in the first group of this experiment was due to the fact that in this case, the pedicles of the testes were separately ligated so that some pressure could be exerted by the intraperitoneal organs on the inguinal canal. Yet the presence of an epididymis or a glass bead in the scrotum resulted in an even more pronounced enhancement of the scrotum-forming action of testosterone (figs. 3, 4, and 5).

It may be said that an additional experiment in which 10 mg. of testosterone propionate were administered daily to immature castrate rats similar to those of group 1 in the above series, also failed to cause complete scrotum formation within 1 month, although this enormous dose enlarged the seminal vesicles and prostates to what might be termed gigantic proportions.

On the basis of the experiments reported in this communication it appears justified to conclude that both the mechanical distention of the scrotum and the stimulating effect of testoid compounds are required for the development of a normal scrotal pouch. Such a synergism between hormonal and mechanical factors has repeatedly been seen to play a role in the induction of morphological changes in accessory sex organs. Thus Selye, Borduas and Masson ('42) found that the musculature of the uterine wall exhibits much more pronounced development in progesterone treated rats if the lumen of the uterus is mechanically distended than if it is collapsed. Similarly Selye and Clarke ('42) demonstrated that while under normal conditions progesterone causes mucification of the vaginal epithelium in spayed rats it elicits cornification of the surface lining if the vaginal lumen is subjected to mechanical distention.

SUMMARY AND CONCLUSIONS

Experiments on castrate albino rats indicate that testosterone in itself does not induce full scrotal development in immature rats nor does it completely inhibit scrotal involution in gonadectomized adults unless the scrotum is mechanically distended. Distention by the epididymis or an "artificial glass testis" can sensitize the scrotum to the action of testosterone. Without this mechanical stimulus the scrota of castrate rats remain subnormal even though the animals receive testosterone in doses sufficient to develop the seminal vesicles and prostates far beyond their normal size.

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LITERATURE CITED

ANDREWS, FREDERICK N. 1940 Thermo-regulatory function of rat scrotum. I. Normal development and effect of castration. Proc. Soc. exper. Biol. a. Med., vol. 45, pp. 867–869.

CLARKE, ELEANOR, AND HANS SELYE 1942 The action of steroid compounds on the vaginal epithelium of the rat. Amer. J. Med. Sci., vol. 204, pp. 401–408.

HAMILTON, J. B. 1936 Endocrine control of scrotum and "sexual skin" in male rat. Proc. Soc. exper. Biol. a. Med., vol. 35, pp. 386–387.

——— 1938 The effect of male hormone upon the descent of the testes. Anat. Rec., vol. 70, pp. 533–541.

KEARNS, WALTER M. 1939 The clinical application of testosterone. J. Amer. Med. Assoc., vol. 112, pp. 2255–2258.

MCCULLAGH, E. PERRY, AND F. J. MCGURL 1939 Further observations on the the clinical use of testosterone propionate. J. Urology, vol. 42, pp. 1265–1273.

——— 1940 Effects of testosterone propionate on epiphyseal closure, Na and Cl balance and on sperm counts. Endocrinology, vol. 26, pp. 377–384.

PHILLIPS, RALPH W. 1935 The development of the tunica dartos muscle. XV. Internat. Physiol. Cong. Leningrad-Moscow.

PHILLIPS, RALPH W., AND FREDERICK N. ANDREWS 1936 The development of the testes and scrotum of the ram, bull and boar. Massachusetts Agricultural Experiment Station Bull. No. 331.

SELYE, HANS, ADRIEN BORDUAS AND GEORGES MASSON 1942 The role of progesterone and local trauma in the production of cystic-glandular changes in the endometrium and hypertrophy of the myometrium. Endocrinol., vol. 30, pp. 71–73.

STEINACH, E., AND H. KUN 1940 Hyperaemia as a test of male sex hormone. Lancet, vol. 238, pp. 688–689.

TYRRELL, WILLIAM P., FREDERICK N. ANDREWS AND MAX R. ZELLE 1942 Effect of post-pubertal castration on thermo-regulatory function of rat scrotum. Endocrinology, vol. 31, pp. 379–383.

PLATE

PLATE 1

EXPLANATION OF FIGURES

1 (Reading from left to right.) Dissected scrotum of intact male, castrate male treated with testosterone and untreated castrate male. Note that in these prepubertally castrated rats testosterone failed to cause scrotal development in the absence of the gonad.

2 (Reading from left to right.) Dissected scrotum of intact male, castrate male treated with testosterone and untreated castrate male. Note that in postpubertal castrates the involution of the scrotum is somewhat inhibited but not prevented by testosterone propionate.

3 Scrotal region of prepubertally castrated rat treated with testosterone propionate. Note very slight degree of scrotal development.

4 Treatment as in the rat shown in figure 3 but epididymis not removed at time of castration. Note that due to the presence of this organ testosterone caused almost normal scrotal development.

5 Treatment as in the rat shown in figure 4 but glass beads substituted for testes. Note that this additional mechanical distention sensitized the scrotum to testosterone sufficiently to make normal scrotum development possible.

PLATE 1